Letters to the Editor

Correspondence re: E. T. H. Fontham *et al.*, Lung Cancer in Nonsmoking Women: A Multicenter Case-Control Study. Cancer Epidemiol., Biomarkers & Prev., *1*: 35–43, 1991

Letter

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Fontham *et al.* (1) have recognized that the misclassification bias may have resulted in biased overestimates of the relative risk of lung cancer due to passive smoking or exposure to ETS.[1] That indeed such misclassification occurs is highlighted in the findings of Fontham *et al.*, who reported individual urinary cotinine/creatinine values as high as 14,014 ng/mg in one group of presumably never-smoking controls and as high as 5,163 ng/mg in another group of controls. While nonsmokers typically have such urinary values below 10 ng/mg, Fontham *et al.* used a cutoff value of 100 ng/mg to eliminate from the reported never-smokers those who very likely did not belong in that class.

In their study, Fontham *et al.* used two kinds of controls for their female lung cancer cases: women who had colon cancer and women chosen from the general population. In principle, a passive-smoking investigation should be limited to never-smoking women and, if the actual smokers in the study could be eliminated, the resulting estimate of the relative risk due to passive smoking would be the more valid.

For lung cancer cases, next-of-kin information was obtained in 34% of instances, yet for only 10% of colon cancer controls. The possibilities for bias due to this alone could be extravagant. But that use of next-of-kin information leads in turn to yet another source of bias: urinary cotinine/creatinine determinations could not or were not made for women for whom next-of-kin information was obtained. There were 134 such lung cancer cases but only 32 such colon cancer controls.

As it turned out, the urinary cotinine/creatinine values were much more moderate for the lung cancer cases than for colon cancer or for population controls. Only two lung cancer cases were excluded for being above the cutoff value of 100 ng/mg, those two being at 131 and 219 ng/mg. Of the 260 colon cancer controls for whom such biochemical determinations were made, seven were above the critical value, their values ranging from 145 to 5163 ng/mg, while among 684 population control biochemical determinations, 14, ranging from 103 to 14,014 ng/mg, were above the 100 ng/mg critical level.

To see how this would bias the estimated relative risk, consider that we removed all the current or ex-smokers from among the presumably nonsmoking controls, but none of those from among the lung cancer cases. The misclassification bias would then be worse than if we did nothing, and to an extent that is true if we make such exclusions more certainly from among controls than from among lung cancer cases. And to the extent that Fontham *et al.* have recognized, by trying to correct for it, that the misclassification bias exists, they are conceding that the apparent increased risk due to ETS could be artificial.

To go on: the report by Fontham *et al.* gives me fresh cause for concern. To bring out an increased relative risk from ETS, these investigators switched their attention from all lung cancers to only adenocarcinomas of the lung. No separate attention was focused on other lung cancers, particularly not on squamous cell carcinomas.

If these investigators have had their choice of which type of lung cancer to emphasize, their statistical significance levels should be modified to take the multiple-testing aspect into account. Apparent statistical significance at the 0.05 level would no longer be at the 0.05 level. And even so, the individual comparisons made by Fontham *et al.* are not statistically significant; it was only by going to trend tests, admittedly a sensible approach, that statistical significance could be achieved.

For household exposure to ETS the relative risk of 1.38 for adenocarcinoma would be reduced to 1.21 for all lung carcinomas. That of 1.43 for more than 30 years of household exposure relative to adenocarcinoma would be reduced to 1.25 relative to all lung carcinomas. Even the significant trend test with $P = 0.03$ would become nonsignificant at $P = 0.14$ if such reemphasis were made.

With the bulk of the lung carcinomas found being adenocarcinoma (281 of 359 by review diagnosis, 244 of 359 by hospital diagnosis), this reduction in the level of significance with the addition of the squamous cell and other lung carcinomas lends itself to an unusual interpretation. It may well be that for these other lung cancers not only are they not associated with ETS, they may even be negatively associated with ETS. And these others, particularly squamous cell carcinomas, are just the ones most strongly associated by others with ETS.

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[1] The abbreviation used is: ETS, environmental tobacco smoke.

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Reply

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Dr. Mantel focuses attention on the urinary cotinine values of the relatively few controls (21 of 944) who reported themselves to be nonsmokers but who were probably active smokers. The fact that these individuals were identified and excluded from the analysis can only be considered a strength of the study. The distribution of cotinine values in this study is quite similar to those reported in the 10-country collaborative study by the International Agency for Research on Cancer of self-report and biochemical indicators of ETS exposure (1). In that study, 1.9% of the reported nonsmokers had urinary cotinine/creatinine values above 100 ng/mg, compared to 1.99% in our study (0.8% of lung cancer cases, 2.7% of colon cancer controls, and 2.0% of population controls). The lower proportion of cases with cotinine levels above 100 ng/mg as compared to colon cancer controls or population controls may well be a result of the prior medical record reviews and physician query used to screen out "ever smokers" from the lung cancer case and colon cancer control series. The information was more commonly available from these sources for patients with lung cancer than with colon cancer, and a larger proportion of potential cases were excluded as ineligible prior to obtaining either interview or urine specimen. Among eligible study subjects the levels of urinary cotinine are quite consistent with previous findings (see Table 1). The somewhat higher current exposure to ETS found among the population controls is not surprising since their mobility is not limited by disease.

Because a 3-tiered approach was used to determine smoking status, information on study subjects' personal use of tobacco was obtained first from the medical record of lung cancer cases and colon cancer controls, then from the study subject's personal physician, and later from the next-of-kin respondent. The information obtained from the medical record and the physician was almost always originally provided by the study subject herself; therefore, in the case of a study subject unable to personally respond or provide a urine sample, her status as a never smoker was obtained from multiple sources, and she was considered eligible only when there was agreement among sources. This approach greatly minimized the possibility of including smokers or ex-smokers.

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In response to Dr. Mantel's concerns about misclassification bias, interviews were conducted with next-of-kin respondents to obtain information about 34% of the lung cancer cases and 10% of the colon cancer controls because the study subjects themselves were either deceased or too ill to respond, a reflection of the survival differential for these two types of cancer: a 72% 1-year survival rate for women with colon cancer as compared to 41% for lung cancer (2). The estimates of relative risk did not differ in analyses restricted to self or proxy respondents.

The association between active smoking and lung cancer is well established for all the main histological types of lung cancer, including adenocarcinoma and large cell, small cell, and squamous cell carcinomas, with differences only in the magnitude of the risk (3). One of the specific aims of this study was to evaluate the histological specificity of the ETS-lung cancer association by examining the relationship for each of the main histological types. We did not have our choice of which histological type to emphasize because most cases turned out to be adenocarcinomas after histological review. The number of squamous cell, large cell, and small cell carcinomas was insufficient to achieve reasonable statistical power in histological type-specific analyses. The very high proportion of adenocarcinomas, consistent across all five study centers, was an unanticipated and interesting finding, even though it is known that adenocarcinoma is the predominant cell type in nonsmokers and in all women regardless of smoking history. The number of cases with large cell, squamous cell, and small cell carcinomas will increase with the 2 additional years of study, but if the present trend continues, they will likely remain a relatively small proportion of the total lung cancer cases.

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Letter

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Fontham and her colleagues report results from the largest case-control study of ETS and lung cancer, which they claim "provide additional evidence in favor of a causal relationship between exposure to ETS and lung cancer in women who have never used tobacco themselves." Although the study has advantages over previ-

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ously published studies in a number of respects, it is important to realize that it has a number of limitations which affect interpretation.

One limitation is that it is an interim report, representing the findings of the first 3 years of a 5-year study, so that, even for the subjects considered, some data (on cotinine and on type of lung cancer) are incomplete. More seriously, no use at all has been made, at this stage, of data collected on such other risk factors as occupation, diet, medical history, and other exposures of interest, so that a potential confounding of ETS with some of these factors has not been taken into account. Two recent studies (1, 2) have demonstrated substantially reduced dietary β-carotene levels in nonsmokers in relation to ETS exposure and have estimated that confounding of the ETS/lung cancer relationship from this source alone could bias the relative risk upward by 10% or more, and it seems plausible that adjustment for this and other confounding variables might have substantially reduced, and made statistically insignificant, the observed associations of lung cancer with various indices of ETS exposure.

Failure to take into account what might be termed "relevant denominators" is another source of potential confounding. Thus the analysis of spousal exposure is not limited to married women, the analysis of occupational exposure is not limited to working women, the analysis of social exposure is not adjusted for number of social occasions, and so on. This leads to an inevitable confusion of possible effects of ETS with possible effects of marital status, occupation, and sociability (and their correlates).

An explicit attempt has been made in this study to minimize bias due to misclassification of active smoking status. However, the procedures used seem in fact to be of limited value. Using smoking data from the medical record and from the physician, which would normally have been provided by the subject, is not of much use in validating statements by the subject. Independent statements by the next of kin or colleagues at work would have been more valuable. Urinary cotinine taken from women with lung cancer is also less useful than it might seem, since many would have given up smoking after contracting the disease. In any case, urinary cotinine does not reflect past smoking.

It is claimed that the possibility of recall bias is minimized by the use of colon cancer controls who, compared with the cases, are "similarly motivated to recall earlier exposures." In view of the attention given in the media to ETS as a possible cause of lung cancer, but not colon cancer, this seems arguable, and the possibility of recall bias is heightened by the large difference in the proportion of next-of-kin respondents providing data (34% for cases and 10% for colon cancer controls).

It is claimed that the association of ETS with lung cancer was specific for adenocarcinoma of the lung. Is this in fact true? Table 6 of the Fontham article gives a relative risk for household exposure for adenocarcinoma of 1.38 (95% confidence interval, 1.04–1.82) and for all lung cancer of 1.21 (0.96–1.54), from which I estimate (approximately) a relative risk of 0.95 (0.65–1.35) for nonadenocarcinoma, which is not significantly different statistically from that for adenocarcinoma, thus failing to justify the special attention given to the adenocarcinoma results.

It would indeed be remarkable if ETS were really to increase the risk of adenocarcinoma by 50% as claimed, given that the association of active smoking with adenocarcinoma is so weak, and given the much lower exposure to smoke constituents from ETS than from active smoking.

Particular attention is given to the dose relationship for lung cancer risk in relation to pack-years of exposure from the spouse, and it is stated that "a dose response, not likely due to chance, was apparent for exposure to tobacco smoke during adult life from a variety of exposure sources." When one examines the data shown in Table 6 of Fontham *et al.* a different impression is given. Within the exposed categories, a tendency for response to rise smoothly with increasing exposure is only seen in two of the eight dose-response relationships, and even in these two the trend is clearly not significant. One gets the impression that the reason the authors chose specifically to present in graphical form results for spouse pack-years of exposure was that this was the index (of many tried) that best showed a smooth relationship. It would have been better had they not overemphasized one specific relationship selected *a posteriori*.

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Reply

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Dr. Lee raises several issues with regard to our report on ETS and lung cancer. His first concern is that it is an interim report, representing 3 years of a 5-year study. We felt at the time, and remain convinced, that the availability of a large data set with which to address an unresolved issue of great public health importance was compelling justification for publishing a report. Data based on cotinine analysis and histopathological review were not complete for all study subjects at the time of submission. Assuming the proportion of study subjects

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found to be ineligible as a result of the procedures completed to date, few if any changes would be expected in the eligible case and control series: one additional case after pathology review, and one case, two colon controls, and two population controls after completion of cotinine analysis might be excluded, a total of six possible study subjects of 1551.

Many, but certainly not all, potential confounders were considered in the analyses, including age, race, geographic region, respondent type, income, and education. Only age had a significant effect on the observed relationships. Given the large number of study subjects exposed to ETS and the relatively small number with occupational, medical, or "other" risk factors, it is unlikely that confounding by these factors would either substantially reduce or elevate the observed associations. The effects of these risk factors will be examined in further analyses. We are doing an extensive analysis of dietary factors, in particular fruits and vegetables, fats, and antioxidant micronutrients including β-carotene. Potential confounding of the ETS lung cancer relationship by relevant dietary factors will be evaluated. It does not appear that dietary intake of β-carotene is related to the spouse's smoking habits in our study. Mean daily intake of β-carotene does not significantly differ between study subjects whose spouse smoked and those whose spouse never smoked. This is true for the total pool of study subjects and after stratification by case-control status. This is, of course, only one indicator and does not eliminate the possibility of some confounding, but suggests that effects, if any, are not likely to be major.

Dr. Lee suggests that the "relevant" denominators are not all female lifetime never smokers at risk of lung cancer with and without exposure, but rather female lifetime never smokers with exposure and a subset without exposure (e.g., married, but spouse did not smoke) after excluding another subset without exposure (e.g., never married, therefore not exposed to spouse who smoked). The relevance of a denominator selected in this fashion is debatable. That aside, restricting analysis to ever-married women had a minimal effect on the total sample size or on estimates of risk. Ten of 420 cases (2.4%) and 43 of 1131 controls (3.8%) had never been married. The risk estimates excluding these study subjects were 1.18 compared to 1.21 in the original analysis for all lung cancer and 1.32 compared to 1.38 for adenocarcinoma associated with exposure to ETS from a smoking spouse. In our series, 135 women had never been employed (50 cases and 85 controls). The estimates of risk associated with occupational ETS exposure among ever-employed women were 1.62 compared to 1.34 in the original analysis for all lung cancer and 1.84 for adenocarcinoma of the lung compared to 1.44.

Information on smoking status was obtained from the medical record, physician, and study subject in a tiered approach. The data obtained from each source were usually originally provided by the study subject, the most knowledgeable source, in response to different questions from different individuals during different time periods, with a consistent response of "never smoked" required. The chart response was not used to validate the subject or next-of-kin response but to eliminate "ever smokers" from the pool for further inquiry. Dr. Lee accurately points out that urinary cotinine is an indicator of current, not past, smoking status, as clearly stated in our report.

Whether recall bias is minimized, eliminated, or exaggerated by the choice of a particular control group is problematic in any epidemiological study. Dr. Lee's point was again clearly stated in the text: "The internal consistency of the findings with the two control groups suggests that recall bias resulting from a diagnosis of cancer is not a likely explanation of the observed effect. The possibility remains that nonsmoking women with lung cancer and nonsmoking women with colon cancer are not similarly motivated to remember exposures to the tobacco smoke of others." The larger proportion of next-of-kin respondents providing data for lung cancer cases (34%) than for colon cancer controls (10%) reflects the realities of the two diseases: the 1-year survival rate for white women with colon cancer is 72% compared to 41% for lung cancer (1). As reported, the estimates of relative risk were similar regardless of respondent type.

A strong association of active smoking has been reported for all types of pulmonary carcinomas including squamous cell, small cell, and adenocarcinoma, differing only in the magnitude of the effect (2). The special attention given to adenocarcinoma is warranted in view of the fact that 78% of the reviewed cases in female never smokers were adenocarcinoma, a remarkably high proportion. The differences in composition of mainstream and sidestream smoke have been well described (3). That exposure to sidestream smoke might result in a distribution of histological types of lung cancer different from that associated with exposure to mainstream smoke is biologically plausible.

Dose (cigarettes/day), duration (years), and an index of dose and duration (pack-years) were selected *a priori* as indicators of exposure from an individual (spouse, mother, father, other household members). Duration is more easily quantified in a setting where "dose" is provided from multiple individuals. That was the rationale for the selection of duration as an indicator of ETS exposure in such settings as shown in Table 6.

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